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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,390	HANS ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11,19-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,19-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 11/10/05 in response to the non-final Office Action mailed 07/15/05.

Status of Claims

2) Claims 10, 19-22 and 28 have been amended via the amendment filed 03/01/04.

Claims 10, 11, 19-24 and 26-29 are pending and are under examination.

The Steidler Declaration

3) Acknowledgment is made Applicants' submission of the Steidler declaration filed 11/10/05. The declaration has been fully considered.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) to Specification

6) The instant specification is objected to for the following reasons:

(a) The use of the trademarks has been noted in this application. For example, see line 1 of page 19: 'Blotto'; and the last line of page 13: 'Qiagen'. The recitation should be capitalized wherever it appears. See M.P.E.P 608.01(V) and Appendix I. Although the use of trademarks is permissible in patent applications, the propriety nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

(b) The specification is objected to for failing to provide proper antecedent basis for the

claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o).

Claim 10, as amended currently, includes the added limitations: 'of a subject' and 'to the subject', which do not have antecedent basis in the specification. Appropriate correction is required.

Rejection(s) Withdrawn

7) The rejection of claim 10 made in paragraph 12(a) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

8) The rejection of claim 19 made in paragraph 12(b) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claim 20 made in paragraph 12(c) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn.

10) The rejection of claim 21 made in paragraph 12(d) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claim 22 made in paragraph 12(e) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claim 28 made in paragraph 12(f) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claims 11, 19-24 and 26-29 made in paragraph 12(g) of the Office Action mailed 07/15/05 under 35 U.S.C. § 112, second paragraph as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

14) The rejection of claims 10, 11, 19-24, 27 and 29 made in paragraph 14 of the Office Action mailed 07/15/05 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (US 6,221,840) in view of Le Page *et al.* (US 6,221,648) or Steidler *et al.* (US 6,605,286), Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993, already of record) (Wells *et al.*, June, 1993) and Tran *et al.*

(*Gut* 44: 636-642, May 1999), is withdrawn upon further consideration. Applicants' arguments with respect to this art rejection have been considered but are moot in view of the withdrawal of and/or the new ground(s) of rejection.

15) The rejection of claim 26 made in paragraph 15 of the Office Action mailed 07/15/05 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (US 6,221,840) as modified by Le Page *et al.* (US 6,221,648) or Steidler *et al.* (US 6,605,286) or Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993, already of record) (Wells *et al.*, June, 1993) and Tran *et al.* (*Gut* 44: 636-642, May 1999) as applied to claim 10, and further in view of Silk (WO 82/03329, already of record), is withdrawn upon further consideration. Applicants' arguments with respect to this art rejection have been considered but are moot in view of the withdrawal of and/or the new ground(s) of rejection.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

16) Claim 10 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 10, as amended, includes the limitation: A method of treatment of intestinal disorders 'of a subject', comprising the oral administration of a recombinant microorganism expressing a trefoil peptide *in vivo* 'to the subject'. Applicants do not point to a specific part of the specification which provides descriptive support for the added limitation. The specification at lines 14 and 15 of page 7 describes that the 'individual' to which the microorganism is administrated may be 'a human or an animal'. However, the specification does not provide descriptive support for the claimed method of treatment of intestinal disorders 'of a subject' wherein a recombinant microorganism expressing a trefoil peptide *in vivo* is orally administered to 'a subject'. The subgenus 'human' or 'animal' does not provide support for the full scope of the generic term 'subject', which encompasses non-human and non-animal subjects. *In re East and Harman* (CCPA) 181 USPQ 716 (May 9, 1974) – claims of a reissue application are drawn to new matter since they broadly recite genus of 'carrier particles' which is not disclosed in original patent, which discloses only subgenus of 'magnetic carrier particles' and species of 'iron, ferrites, nickel, and cobalt' carrier particles. Therefore, the above-identified new limitations in the claim(s) are considered to be new matter. *In*

re Rasmussen, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitations, or to remove the new matter from the claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

17) Claims 10, 11 and 19-29 are rejected under 35 U.S.C § 112, first paragraph, because the specification while being enabling for a method of treating DSS-induced acute colitis in a murine subject comprising intragastric administration to said mice of a minimum of 10^8 cells of a recombinant *Lactococcus lactis* comprising a vector that comprises the TEF1-coding nucleotide sequence under the control of a suitable promoter sequence and a suitable secretion signal sequence and expresses the TEF1 trefoil peptide in the colon, does not reasonably provide enablement for a method of treatment of any intestinal disorders other than DSS-induced acute colitis in any human or non-human subject comprising the oral administration of any generic 'recombinant microorganism' expressing any trefoil peptide anywhere *in vivo* in the subject, as claimed in a broad sense. Furthermore, independent claim 10 lacks limitations of the critical element that is required to practice the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instantly claimed invention is drawn to a method of treatment of intestinal disorders of a subject comprising the oral administration of a recombinant microorganism expressing a trefoil peptide *in vivo* to the subject. See claim 10. The term 'intestinal disorders' is not limited to those

with lesions or those localized to colon, or to acute colitis, ulcerative colitis, or Crohn's disease, but includes a plethora of intestinal disorders of microbial and non-microbial pathogenesis, environmental and genetic causes as well as infectious, inflammatory, immunologically-mediated, allergic, and cancerous intestinal disorders, with or without involving lesions, occurring in any part of the intestine of a human or non-human subject. Non-inflammatory intestinal disorders, intestinal metaplasia, radiation-induced or chemotherapy-induced intestinal lesions or disorders, intestinal disorders of obscure origin, traveller's disease, stress-induced disorders etc. are encompassed within the scope of the broad limitation 'intestinal disorders'. The broadly recited term 'a recombinant microorganism' in claim 10 encompasses any microorganism other than *Lactococcus lactis*, including fungi, parasites, yeasts, aerobic and anaerobic bacteria, Gram-positive and Gram-negative bacteria, *Chlamydia*, *Rickettsia*, *Spirochetes* etc. The term 'a recombinant microorganism' encompasses both pathogenic and non-pathogenic microorganisms. A pathogenic microorganism expressing a trefoil peptide would most likely be pathogenic and therefore harmful to a subject as opposed to being therapeutic. The term '*in vivo*' is not limited to colon, but broadly encompasses any *in vivo* location along the oral route, including the oral cavity. A review of the instant application indicates a lack of enablement for this broadly claimed method.

A review of the instant specification indicates that the enabling disclosure in the instant application is limited to a therapeutic showing in an *in vivo* mouse model of DSS-induced acute colitis in which DSS-treated mice were intragastrically administered, from day 1 to day 7, with 1.10^8 cells of one specific recombinant *Lactococcus* species, *L. lactis,* expressing a specific trefoil peptide, mouse TEF1. See Example 2. In this DSS-induced acute colitis murine model, a showing of the therapeutic effect of recombinant *L. lactis* expressing mTEF1, as measured by 'a significant reduction of the inflammation of more than 65%', or a significantly decreased intestinal inflammation, or inflammatory infiltration and the epithelial damage, is limited to the location, 'colon', of the treated mice. See paragraphs [0078] through [0081]. The 132 Steidler declaration filed 11/10/05 provides further evidence, which is also limited to a showing in a DSS-induced acute colitis mouse model, of the therapeutic effect of a daily intragastric inoculation of 2×10^9 CFU of a recombinant *L. lactis* expressing a trefoil peptide, as indicated by reduced epithelial damage and inflammatory infiltration by 50%. DSS-induced acute inflammatory colitis in mice however is not representative of the full scope of the broadly recited 'intestinal disorders of a subject', which

encompasses a plethora of non-DSS-induced intestinal disorders, non-inflammatory intestinal disorders, cancerous intestinal disorders, infectious intestinal disorders, radiation-induced intestinal disorders, Crohn's disease, ulcerative colitis etc. There is no indication in the instant specification that the DSS-induced acute colitis murine model is the art-accepted animal model for Crohn's disease or colitis ulcerosa. Similarly, one recombinant trefoil peptide-expressing species of the genus *Lactococcus*, i.e., *Lactococcus lactis*, is not representative of the full scope of the large genus: 'a recombinant microorganism', 'a bacterium', 'a bacterium of a food grade gram-positive bacterial strain', '*Lactobacillus* species', and '*Lactococcus* species'. The state of the art at the time of the invention established that one of skill in the art cannot use any and every 'microorganism' to recombinantly express a medically important heterologous protein for *in vivo* administration for therapeutic or prophylactic purposes. For example, in 1996, Lothar Steidler disclosed two recognized problems with the use of *Escherichia coli*, the most established and well studied microorganism, for recombinant expression of a scientifically and commercially important heterologous protein: (a) the presence in its cell wall of the undesired lipopolysaccharide or LPS which are known in the art to be 'extremely pyrogenic' leading to the death of laboratory animals by the induction of systemic inflammatory responsive syndrome and which are known in the art to strongly mask any lymphokine effect; and (b) the formation of inclusion bodies resulting in an inactive or non-refoldable protein and its secretion into the periplasm. See pages 63 and 64 of Lothar Steidler (*Lactic Acid Bacteria*: *Current Advances in Metabolism, Genetics and Applications*. (Ed) Bozoglu TF *et al.* NATO ASI Series. Vol. H98. Springer Verlag, Berlin Heidelberg, pages 63-79, 1996). Furthermore, it has been established in the art that not all *Lactobacteria* are capable of expressing sufficient quantities and/or suitable forms of a heterologous antigen *in vivo* so as to elicit a beneficial effect *in vivo,* especially when administered orally. Although paragraph [012] of the instant specification exemplifies several species and subspecies of *Lactococcus* and *Lactobacillus*, there is no concrete showing that all these species and subspecies of *Lactococcus* and *Lactobacillus*, or a representative number of these species and subspecies if used to express a trefoil peptide recombinantly, would be effective in treating any intestinal disorders in any subject upon oral administration. The art reflects unpredictability in this regard in that not all recombinant lactobacilli, let alone 'a recombinant microorganism' generically recited in claim 10, a 'bacterium' as recited in

claim 19, or 'a gram-positive bacterial strain' as recited in claim 20, express sufficient amounts of a heterologous antigen in a form suitable for presentation to a subject's immune system and elicit the desired beneficial response when administered to said subject *orally*. For instance, Wells *et al.* (*Antonie van Leeuwenhoek* 70: 317-330, 1996) showed that recombinant *L. plantarum* 80 expressing *E. coli* beta-galactosidase, when administered orally to mice four times, did not elicit a significant response in mice. However, when the same recombinant *L. plantarum* 80 was administered intraperitoneally, the recombinant elicited a significant response (see paragraph bridging pages 322 and 323). The art documents a similar showing with regard to orally administered recombinant Gram positive bacteria other than lactobacteria. For instance, recombinant staphylococci expressing heterologous peptides and proteins on their surface elicited highly variable responses in mice even after a total of 24 oral inoculations when compared with a subcutaneous inoculation of the recombinant staphylococci. See the first two full paragraphs in the right column of page 323 of Wells *et al.* (1996). The art also established that not all species of *Lactobacteria* can express a heterologous antigen in a proper form or assembly presentable to a host. Slos *et al.* (*FEMS Microbiol. Lett.* 169: 29-36, 1998) showed that when *L. plantarum* was recombinantly modified to secrete a bacterial protective antigen, the antigen so secreted failed to bind its receptor, indicating that the recombinant antigen expressed was not assembled or folded properly. See second full paragraph in left column on page 30 and paragraph bridging pages 35 and 36 of Slos *et al.* Furthermore, a post-filing publication by Shaw *et al.* (WO 01/21200) taught the lack of efficacy of a *Lactobacillus casei*-based expression system as an *in vivo* carrier of heterologous antigens. Shaw *et al.* discuss the report of Pouwels *et al.* showing how expression vectors in *Lactobacillus casei* achieved good expression of a heterologous antigen, yet only provided a fairly low level effect after 'oral' introduction. See paragraph bridging pages 5 and 6; and first two full paragraphs on page 6. Even in 2001, i.e., about two years after the effective filing date of the instant application, Shaw *et al.* provided the teaching that extrapolation of data in this field between different species of *Lactobacillus* is not always reliable (see second full paragraph on page 6 of *Lactobacillus*). Shaw *et al.* concluded that the variations in both the levels of heterologous protein expression, sustainable levels of degraded heterologous protein, and the persistence in the GI tract between the recombinant strains can have pivotal influences on the potency of the recombinant *Lactobacillus* species and account for the often surprising observations distinguishing the two strains (see lines 19-23 of page

39). With these reports on art-recognized unpredictability, one of skill in the art would look into Applicants' original disclosure for specific guidance, which in the instant case is limited to a recombinant *L. lactis* and its use in the claimed method of treatment. With the exception of a recombinant *Lactococcus lactis* strain expressing mouse TEF1 trefoil peptide, Applicants have not enabled a method of treatment of any intestinal disorders, with or without lesions, in any subject, human or non-human, by oral administration of any recombinant microorganism expressing any trefoil peptide anywhere *in vivo* in said subject, as claimed broadly.

Furthermore, there is no showing that one of skill in the art can practice the instantly claimed method of treatment of intestinal disorders in human or non-human subjects by oral administration of 'a' (i.e., single) recombinant microorganism expressing a trefoil peptide *in vivo,* as recited in claim 10. There is no showing however that 'a' single recombinant microorganism, a single bacterium, a single food grade gram-positive bacterial strain, a single *Lactococcus* or *Lactobacillus,* or a single *Lactococcus lactis* cell expressing 'a' trefoil peptide molecule or TEF1 in particular, is able to treat any of the broadly recited 'intestinal disorders' of microbial or non-microbial pathogenesis, or inflammatory or non-inflammatory causes including Crohn's disease, ulcerative colitis, or acute colitis, on oral administration to a subject. The term '*in vivo*' broadly encompasses any *in vivo* location along the oral route. There is no showing that a single recombinant *L. lactis*, let alone any recombinant microorganism, is able to express and/or deliver adequate quantities of the trefoil peptide to reach the colon, i.e., the site of acute colitis, in order to induce a therapeutic effect. It is highly unlikely that a trefoil peptide delivered via an orally administered single *L. lactis* cell or any other single recombinant microorganism expressing such a trefoil peptide, would survive early and irreversible inactivation during passage through acidic and proteolytically active stomach and reach the site of the disorder or lesion, i.e., intestine or colon, in a stable form and therapeutically adequate amount. This is particularly important because *L. lactis* is recognized in the art as an oral commensal bacterium, which lacks any known capacity to multiply *in vivo* except in gnotobiotic mice, and is known to pass through the enteric tract of humans in a transitory fashion without any evidence of colonization. See left column on page 3183 of Steidler *et al.* (*Infect. Immun.* 66: 3183-3189, 1998). This is critically important because in their response filed 11/10/05, Applicants emphasize the importance of the quantity of the TEF peptide expressed *in vivo* by the recombinant

L. lactis and the availability of the expressed peptide in the colon. In the last paragraph on page 9 of their amendment/remarks filed 11/10/05, Applicants submit the following:

> .... the state of the art at the time of filing of the present application indicates that microbial delivery of TEF peptides would not have a reasonable expectation of success since it could not guarantee that sufficient amount of the peptides could be delivered to the desired site.

On page 10 of their amendment/response, Applicants emphasize the quantities of TEF peptides required to induce a therapeutic effect. Applicants discuss Poulsen's (*Gut* 43: 240-247, 1998, submitted by Applicants) clear teaching at the effective filing date of the present application, that oral administration of TEF peptides might be problematic and might not effectively deliver the TEF peptides to the site of action. Paragraph [0074] of the specification describes the importance of intragastric inoculation of the necessary amount of recombinant cells each day for treatment of mice. Paragraph [0075] of the specification describes that a minimum of 1.10^8 cells of *L. lactis* are inoculated by means of a gastric catheter from day 1 until day 7 of the DSS treatment of mice. These mice so inoculated or treated are described as showing histologic improvement in the colon by showing a significant decrease in inflammatory infiltration and the epithelial damage. See paragraphs [0078] to [0081]. Both from the specification and the Steidler declaration, as well as from the knowledge in the art at the time of the invention, it is clear that the amount of recombinant mTEF1-expressing *L. lactis* administered intragastrically is critical to practice the invention. Instant claims however lack a limitation on the therapeutically effective amount of the recombinant microorganism or even recombinant *L. lactis* administered orally or the trefoil peptide expressed by said recombinant at the site of DSS-induced acute colitis. The independent claim 10 lacks limitations of the critical element that is required to practice the invention. None of the instant claims recite the quantity of the TEF peptide expressed *in vivo,* or the quantity of the generically recited recombinant microorganism expressing the trefoil peptide that is administered orally. The feature or element which Applicants describe as being an essential or critical feature of the invention is omitted from the claims. *In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).*

For the reasons delineated above, undue experimentation would have been required by one of skill in the art at the time of the invention to reproducibly practice the full scope of the invention as claimed due to the lack of sufficient and/or specific guidance, the lack of working examples enabling the full breadth of the claimed method, the quantity of experimentation necessary, the art-

recognized unpredictability, and the breadth of the claims. The instant claims are viewed as being non-enabled with regard to the entire scope.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

17) Claims 10, 11, 19-24 and 26-29 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regards as the invention.

(a) Claim 10 is vague and indefinite in the recitation: 'treatment of intestinal disorders' of a subject comprising the oral administration of 'a' recombinant microorganism expressing 'a' trefoil peptide [Emphasis added]. Does it mean that what is orally administered is a single recombinant microorganism expressing a single trefoil peptide molecule in a method of treatment of more than one intestinal disorders occurring in a subject?

(b) Claim 20 is vague, indefinite and/or confusing in the limitation: 'of claim 19, wherein the bacterium is of food grade gram-positive bacterial strain'. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with the limitation --of claim 19, wherein the bacterium is a food grade gram-positive bacterium-- with a concurrent replacement of the limitation 'bacterial strain' in the dependent claim 21 with the limitation --bacterium--.

(c) Claim 28 is vague and indefinite in the limitation 'a nucleotide sequence of SEQ ID NO: 1, 2 or 3', because it is unclear whether what is comprised is the full-length nucleotide sequence of SEQ ID NO: 1, 2 or 3, or a less than a full-length nucleotide sequence of SEQ ID NO: 1, 2 or 3. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3--.

(d) Claims 11, 19-24, and 26-29, which depend directly or indirectly from claim 10, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

18) Claims 10, 11, 19-24 and 26-29 stand rejected.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile

transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

20) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

February, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER